Ionic Liquid–Catalyzed Green Synthesis of Medicinally Relevant Heterocycles

SYNOPSIS

SUBMITTED TO

(Faculty of Sciences)

UNIVERSITY DEPARTMENT OF CHEMISTRY

B. N. MANDAL UNIVERSITY, MADHEPURA

FOR THE DEGREE OF

DOCTOR OF PHILOSPHY

BY

Name: Deepak Kumar

Class Roll No.: 02

Exam Roll No.: CHE-02/22

Email id: chemistry.dpk@gmail.com

Mob No.: 9709139111

B.N.MANDAL UNIVERSITY, LALOO NAGAR, MADHEPURA

SYNOPSIS OF RESEARCH WORK FOR Ph.D. DEGREE IN THE FACULTY OF SCIENCE (CHEMISTRY)

Ionic Liquid–Catalyzed Green Synthesis of Medicinally Relevant Heterocycles

(i) Work Plan

a. Purpose and need of the study

Heterocycles represent one of the most indispensable structural motifs in modern medicinal chemistry, agrochemical development, and advanced material science. A vast number of clinically approved drugs, antimicrobials, anti-inflammatory agents, anticancer molecules, and enzyme inhibitors incorporate heterocycles such as pyrroles, pyrazoles, imidazoles, and triazoles. Despite their importance, traditional synthetic routes for these scaffolds often rely on hazardous organic solvents, corrosive catalysts, and energy-intensive conditions, resulting in significant environmental burden and safety concerns. Increasing awareness of ecological sustainability has accelerated the shift toward greener and cleaner methodologies. Ionic liquids have emerged as powerful alternatives due to their unique combination of negligible vapor pressure, high thermal stability, tunable acidity/basicity, recyclability, and exceptional solvation behavior. Their dual role as solvent and catalyst allows organic transformations to proceed under milder, cleaner, and more efficient conditions while reducing waste generation. Recent studies demonstrate that ionic-liquid-mediated reactions afford higher yields, shorter reaction times, and improved selectivity compared to classical methods. Given their "designer solvent" capability, ionic liquids can be tailored to suit diverse heterocyclic transformations, making them highly relevant for sustainable synthesis. Therefore, the present research proposes to explore ionic-liquid-based catalytic systems for developing efficient, eco-friendly methodologies toward the synthesis of medicinally important heterocycles. This work aims to contribute to green chemistry by designing protocols that are cleaner, safer, and industrially adaptable.

Review of Literature of proposed work

Heterocycles such as pyrroles, pyrazoles, imidazoles, and triazoles display broad biological and pharmacological relevance, prompting continuous development of improved synthetic strategies. Conventional approaches, such as Paal–Knorr condensation, dipolar cycloaddition, and multicomponent reactions, often require harsh conditions, strong acids, or toxic organic solvents. To overcome these limitations, ionic liquids have gained prominence as sustainable media and catalysts for heterocycle construction. Their tunable ionic composition, recyclability, and high solvation efficiency enable enhanced reaction rates, superior yields, and reduced environmental impact. Over the last two decades, numerous ionic-liquid-based methodologies have been reported for assembling heterocycles under homogeneous or heterogeneous conditions. Additionally, various catalysts, such as $Zr(HPO_4)_2$, Fe_3O4 nanocomposites, and supported metal-based ionic liquids, have demonstrated improved efficiency in related heterocycle synthesis. These advances underline the potential of ionic liquids as pivotal tools for green organic synthesis and justify further investigation into their catalytic applications.

b. Details of the project with chapterization

Chapter- I: Introduction

Chapter- II: Survey of previous works

Chapter- III : Experimental

Chapter- IV: Result and Discussion

Chapter- V : Conclusion

Chapter I: Introduction

This chapter will outline the significance of heterocycles in drug discovery, the role of green chemistry in modern synthesis, and the emergence of ionic liquids as sustainable catalytic systems. Key concepts, motivations, and the scope of the proposed work will be presented.

Chapter II: Survey of Previous Works

A comprehensive review of literature related to ionic-liquid-mediated synthesis of heterocycles will be included. Comparisons between classical and green methodologies, existing catalytic systems, and knowledge gaps will be highlighted.

Chapter III: Experimental

This chapter will describe the materials, ionic liquids, catalysts, and detailed synthetic procedures used for preparing various heterocycles. Optimization parameters, reaction conditions, purification methods, and analytical characterization techniques (NMR, FT-IR, MS) will be documented.

Chapter IV: Results and Discussion

Results of optimized reactions, catalytic performance, yields, mechanistic insights, and comparative studies with conventional methods will be presented and critically analyzed. Structure-activity relationships will also be included when applicable.

Chapter V: Conclusion

This chapter will summarize the major findings, highlight the environmental and synthetic advantages of the developed methodologies, and suggest future research prospects..

c. Hypothesis

The central hypothesis of the proposed work is that ionic liquids, owing to their tunable physicochemical properties, can serve as highly efficient, recyclable, and environmentally benign catalysts for the synthesis of medicinally significant heterocycles. By carefully selecting and modifying ionic liquids with appropriate cation–anion combinations, it is expected that reaction efficiency, selectivity, and product yields can be substantially improved under mild conditions. The inherent advantages of ionic liquids, such as high thermal stability, negligible vapor pressure, strong solvation capacity, and the ability to stabilize reactive intermediates, are anticipated to reduce the requirement for harsh reagents and energy-intensive processes. Furthermore, it is hypothesized that ionic-liquid-mediated protocols will offer superior control over regioselectivity and functional-group tolerance, enabling the synthesis of structurally diverse heterocyclic derivatives with potential therapeutic relevance. The recyclability of these catalytic systems is expected to significantly lower reaction cost and environmental load. Therefore, the research aims to demonstrate that ionic liquids can outperform traditional catalysts while adhering to green chemistry principles, ultimately providing scalable, cleaner, and more sustainable synthetic methodologies for heterocycle production.

d. Methodology

The proposed methodology involves the systematic development of ionic-liquid-catalyzed synthetic routes for medicinally relevant heterocycles. The study will begin with selecting suitable ionic liquids based on their acidity/basicity, stability, and solvation properties. Model reactions for each heterocyclic class will be undertaken to evaluate catalytic performance. Optimization studies will be conducted by varying parameters such as ionic liquid type, catalyst loading, solvent or solvent-free conditions, temperature, and reaction time. The goal is to identify conditions that provide maximum yield, high purity, and minimal environmental impact. Reactions will be monitored using TLC, and purified compounds will be characterized by NMR, FT-IR, mass spectrometry, and elemental analysis. Recyclability of the ionic liquids will be examined through repeated reaction cycles to assess catalyst stability and efficiency. Comparative studies with conventional synthetic methods will be performed to demonstrate the advantages of ionic-liquid-assisted transformations. Finally, selected heterocyclic products may be screened for basic biological properties, depending on feasibility.

e. Bibliography

1. Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T. An Update on the Nitrogen Heterocycle Compositions and Properties of US FDA-Approved Pharmaceuticals (2013–2023). *J. Med. Chem.* **2024**, *67*, 11622–11655.
2. Jaiswal, S.; Verma, K.; Dwivedi, J.; Sharma, S. Tetrazole Derivatives in the Management of Neurological Disorders: Recent Advances on Synthesis and Pharmacological Aspects. *Eur. J. Med. Chem.* **2024**, *271*, 116388.
3. Behera, S.; Bera, S. K.; Basoccu, F.; Cuccu, F.; Caboni, P.; De Luca, L.; Porcheddu, A. Application of Bertagnini's Salts in a Mechanochemical Approach Toward Aza-Heterocycles and Reductive Aminations via Imine Formation. *Adv. Synth. Catal.* **2024**, *366*, 2035–2043.
4. Behera, B. K.; Ghosh, P.; Saikia, A. K. Recent Advances in the Synthesis of N-Heterocycles via Lewis Acid-Catalyzed/Mediated Cyclization of Propargyl- and Homopropargyl-Amines and Their Derivatives. *Tetrahedron* **2024**, *162*, 134123.
5. Heravi, M. M.; Zadsirjan, V. Prescribed Drugs Containing Nitrogen Heterocycles: An Overview. *RSC Adv.* **2020**, *10*, 44247–44311.

6. Devi, M.; Jaiswal, S.; Yaduvanshi, N.; Kaur, N.; Kishore, D.; Dwivedi, J.; Sharma, S. Design, Synthesis, Antibacterial Evaluation and Docking Studies of Triazole- and Tetrazole-Linked 1,4-Benzodiazepine Nucleus via Click Approach. *ChemistrySelect* **2023**, *8*, e202204710.
7. Jaiswal, S.; Arya, N.; Kishore, D.; Dwivedi, J.; Sharma, S. Exploring Azetidine-Containing Heterocycles: From Green Synthesis to Applications. *Tetrahedron* **2025**, *174*, 134491.
8. Łowicki, D.; Przybylski, P. Tandem Construction of Biologically Relevant Aliphatic Five-Membered N-Heterocycles. *Eur. J. Med. Chem.* **2022**, *235*, 114303.
9. Ebenezer, O.; Jordaan, M. A.; Carena, G.; Bono, T.; Shapi, M.; Tuszynski, J. A. An Overview of the Biological Evaluation of Selected Nitrogen-Containing Heterocycle Medicinal Chemistry Compounds. *Int. J. Mol. Sci.* **2022**, *23*, 8117.
10. Bhardwaj, K.; Jaiswal, S.; Bhardwaj, A.; Arora, D.; Jain, S.; Kumar, G.; Dwivedi, J.; Sharma, S. Unveiling Novel Thiadiazolo-Annulated Azepine Hybrids as Peptide Deformylase Inhibitors: DFT, Molecular Docking and ADMET Studies. *J. Mol. Struct.* **2025**, *1336*, 142105.
11. Jaiswal, S.; Devi, M.; Yaduvanshi, N.; Jain, S.; Dwivedi, J.; Kishore, D.; Kuznetsov, A. E.; Sharma, S. Identification of New Triazolo-Annulated Dipyridodiazepine Derivatives as HIV-1 Reverse Transcriptase Inhibitors: Design, Synthesis, DFT, Molecular Modelling and In Silico Studies. *J. Mol. Struct.* **2024**, *1314*, 138734.
12. Kedimar, N.; Rao, P.; Rao, S. A. Imidazole-Based Ionic Liquid as Sustainable Green Inhibitor for Corrosion Control of Steel Alloys: A Review. *J. Mol. Liq.* **2024**, *411*, 125789.
13. Sharma, S.; Sharma, P.; Budhalakoti, B.; Kumar, A.; Singh, K.; Kamboj, R.; Bhatrola, K. Exploring the Impact of Ionic Liquids on Pyrazole Derivatives Synthesis: A Critical Review. *ChemistrySelect* **2024**, *9*, e202401925.

Name of Research Scholar: Deepak Kumar
Class Roll No. :- 02

Examination Roll No. :- CHE-02/22

Session :- 2025-2028

Mobile No. :- 9709139111

Email id :- chemistry.dpk@gmail.com

Signature of Research Scholar